BONFILS BLOOD CENTER

Colorado's Community Blood Center

December 26, 2001

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Attention: Indira Hewlett, PhD

RE: Draft Guidance for Industry, December 2001

Dear Doctor Hewlett:

Clarification of the statement in Part IV Implementation should be made. In this part you say that after approval for use of a licensed HIV-1 and HCV NAT, the establishment may continue using an alternative NAT testing under an approved IND. This statement continues; provided that the manufacturer implements the approved test at the same time. It is not clear what the meaning of that statement is. If a licensed Source Plasma operation has access to the now ongoing blood donor IND for HCV and HIV, such as a licensed blood center with a Source Plasma license, this testing should be acceptable in lieu of using the NGI license test or any other test. This is particularly cogent since blood centers are using a 24-donor pool as opposed to a much larger pool in the Source Plasma process.

Sincerely,

W. C. Dickey, MD
President/CEO

WCD/bec

717 Yosemite Circle • Denver, CO 80230 • 303.341.4000

Guidance for Industry

Use of Nucleic Acid Tests on Pooled Samples from Source Plasma Donors to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Submit comments and suggestions regarding this draft document by the date provided in the Federal Register notice announcing the availability of the draft guidance. Submit comments to Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that published in the Federal Register.

Additional copies of this draft guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this draft guidance contact Indira Hewlett, Ph.D., (301) 827-0795.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
December 2001

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Draft – Not for Implementation

GUIDANCE FOR INDUSTRY

Use of Nucleic Acid Tests on Pooled Samples from Source Plasma Donors to Adequately and Appropriately Reduce the Risk of Transmission of HIV-1 and HCV

This guidance represents FDA's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of applicable statutes and regulations.

I. INTRODUCTION

The purpose of this guidance document is to inform you, all establishments, engaged in the manufacture of Source Plasma as defined in 21 CFR 640.60: 1) that we, the Food and Drug Administration (FDA), have approved nucleic acid tests (NAT) to identify human immundeficiency virus type 1 (HIV-1) and hepatitis C virus (HCV) in Source Plasma donations; 2) that we believe that a licensed nucleic acid test to identify HIV and HCV in Source Plasma donations, when available, should be used to adequately and appropriately reduce the risk of transmission of these communicable diseases; and 3) that we expect that a licensed nucleic acid test to identify HIV-1 and HCV in Source Plasma donations will be available after establishments submit biological license application (BLA) supplements providing for the use of an approved nucleic acid test, and after we have approved such supplements. We recommend that you submit pre-approval supplements in accordance with 21 CFR 601.12(b) by June 1, 2002.

II. BACKGROUND

FDA's final rule (66 FR 31146, June 11, 2001) entitled "Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Diseases" becomes effective on December 10, 2001. Section 610.40(b) of that regulation provides that manufacturers "must perform one or more screening tests to adequately and appropriately reduce the risk of transmission of communicable disease" (66 FR 31162). As we noted in the preamble to the final rule, the standard for adequate and appropriate testing will change as new testing technology is approved by FDA. We explained, "we intend to regularly issue guidance describing those tests that we believe would adequately and appropriately reduce the risk of transmission of communicable disease agents" (66 FR 31149).

The availability of nucleic acid testing to identify HIV and HCV will change the testing protocol that should be used to adequately and appropriately reduce the risk of transmission of those diseases. We believe that, when nucleic acid testing is available, it may no longer be appropriate to rely solely on other tests for HIV-1 and HCV, such as those for antibody and HIV-1 p24 antigen; those tests, without nucleic acid testing, may not be adequate and

appropriate. FDA may also consider not requiring HIV-1 p24 testing of Source Plasma if establishments implement NATs that are more sensitive than HIV-1 p24 tests.

Transmission of HIV and HCV by blood and blood products has been dramatically reduced as a result of implementation of sensitive tests for viral antibody and antigen, and in the case of plasma derivatives, the use of effective virus removal and inactivation methods. Sources of remaining risk for transfusion transmission and to plasma pools include window period donations, viral variants, atypical seroconversion and laboratory testing error (Ref 1, 2). A recent report found that paid plasma donors were more likely to donate potentially infectious units (Ref. 3). However, initatives by the source plasma industry, including NAT testing under IND, greatly reduced the chances of these units entering the pools for manufacuring (Ref 3). Although effective viral clearance methods are in place for almost all plasma derivatives, measures to close the window period are expected to further reduce the residual risk of HIV or HCV infectious units entering plasma pools. In 1994, we held a workshop to explore the potential application of nucleic acid based methods to donor screening for HIV. It was felt that although these methods were clearly sensitive, they were not ready for implementation on a large scale at that time. However, the workshop fueled interest in developing systems for implementation of nucleic acid methodology for testing blood and plasma donations.

Subsequently, industry in collaboration with the National Institutes of Health and FDA actively pursued development of NAT systems for HIV-1 and HCV. Due to the cost and labor intensity of NAT, testing of minipools of plasma rather than individual donations seemed to be more feasible and by 1997 some manufacturers in Europe had voluntarily instituted NAT on pooled samples of plasma. At about that time, the European Union issued a directive that by July 1, 1999, HCV ribonucleic acid (RNA) testing would be required in Europe for all plasma for fractionation and that the requirement for HIV-1 RNA testing would follow at a later date. The European directive, which applied to both Source Plasma and recovered plasma, provided impetus to the rapid development of NAT for all blood and plasma donations. In November 1999, FDA announced the availability of the draft document entitled "Guidance for Industry: Application of Current Statutory Authority to Nucleic Acid Testing of Pooled Plasma" for public comment on FDA's approach to regulating nucleic acid testing for infectious disease agents when intended for use in blood donor screening and/or manufacturing of blood products. We also provided the industry with guidance on assay validation and regulatory strategies for licensure of NAT.

We permitted the clinical study of this investigational technology on a large scale. Such large-scale studies were thought to be necessary to demonstrate the efficacy of NAT as a donor screen primarily because the frequency of window period donations is low. Clinical studies to evaluate NAT were initiated in 1997 under approved Investigational New Drug applications (INDs). Data collected under these INDs would support approval of subsequent BLAs. We have worked with manufacturers toward validation of NAT assays for donor screening.

III. AVAILABILITY OF LICENSED NAT FOR SCREENING OF SOURCE PLASMA DONORS

On September 18, 2001, we licensed the first pooled sample NAT system for the detection of HIV-1 and the first pooled sample NAT system for the detection of HCV RNA in Source Plasma donations. National Genetics Institute developed these test systems for screening pooled Source Plasma donations. On the same day, we approved a prior approval supplement submitted by Alpha Therapeutic Corporation, which authorized Alpha to implement the new testing technology. Other manufacturers are currently investigating other NATs for Source Plasma collections.

IV. IMPLEMENTATION

HIV-1 and HCV NAT of Source Plasma involves the use of complex pooling and testing systems. We recognize that the testing technology is not universally available, and that establishments need time to implement these complex systems. Therefore, we recommend that Source Plasma manufacturers submit prior approval supplements to implement HIV-1 and HCV NAT in their establishments by June 1, 2002. You should not implement the testing change until we have reviewed and approved your prior approval supplement. You may continue NAT testing under IND while we review your prior approval supplement. After we approve the supplement for use of a licensed HIV-1 and HCV, the establishment may continue use of alternative NAT testing under an approved IND provided that the manufacturer implements the approved test at the same time. In the meantime, manufacturers who wish to pursue validation of in-house tests should submit INDs and BLAs as appropriate.

V. REFERENCES

1. M.P. Busch and S. H. Kleinman, Nucleic Acid Amplification Testing of Blood Donors for Transfusion-Transmitted Infectious Diseases, Transfusion 2000; 40:143-159.

2. S.H. Kleinman and M.P. Busch, The Risks of Transfusion-Transmitted Infection: Direct Estimation and Mathematical Modeling, Bailliere's Clinical Haematology 2000; 13(4):631-649.

3. General Accounting Office, Blood Plasma Safety: Plasma Product Risks Are Low If Good Manufacturing Practices Are Followed, GAO/HEHS-98-205.

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